REMARKS

I. Status of the Claims

Claims 10 to 13 and 28 are currently pending. Claims 10 to 13 and 28 stand rejected. Claims 10 and 28 are currently amended.

Claim 10 as amended now recites:

A method to diagnose an oral or systemic pathology, disease or disorder in a subject, wherein the disease is a cancer of the oral cavity and/or of oropharynx, the method comprising:
providing a ~~cell-free fluid phase portion of the~~ saliva supernatant from ~~of~~ the subject;
detecting in the ~~provided cell-free~~ saliva supernatant ~~fluid phase portion~~ an mRNA profile of a gene associated with the pathology, disease or disorder, wherein the gene is selected from the group consisting of the gene coding for IL8, DUSP1, H3F3A, OAZ1, S100P and SAT; and
comparing the mRNA profile of the gene with a predetermined human mRNA profile of the gene, the predetermined human mRNA profile of the gene being indicative of the presence of the pathology, disease or disorder in the subject.

Support for this amendment is found throughout the specification and the claims as originally filed, for example, paragraphs [0086], [0087], [00112], [00125], and [00137] and original claims 10 and 11.

Claim 28 as amended now recites:

The method of claim 10, wherein detecting an mRNA profile ~~transcriptome pattern~~ is performed by microarray assay, high density oligonucleotide microarray assay, quantitative PCR or RT-PCR.

Support for this amendment is found throughout the specification, for example, paragraphs [0061], [0063], and [0064].

II. Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 10 to 13 and 28 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. Applicants respectfully disagree.

The instant invention provides methods of diagnosing oral and/or oropharynx cancer. The claimed methodology utilizes saliva supernatant and entails detecting an mRNA profile. The detected mRNA profile is compared to a pre-determined human mRNA profile, wherein the pre-determined profile is an indicator of oral and/or oropharynx cancer.

The instant invention further provides that the mRNA profile of IL8, DUSP1, H3F3A, OAZ1, S100P and SAT can be applied in the diagnosis of the oral cavity and/or the oropharynx cancer.

Thus, the claims can be described as directed to a diagnostic assay.

In assessing enablement of claims directed to methods of diagnosis, the following examination guidelines are to be followed:

> "Unless a specification specifically states something to the contrary, the term 'diagnostic assay' is to be construed to mean any assay that can be used to help diagnose a condition, as opposed to an assay that can, in and of itself, diagnose a condition. A diagnosis is typically made by evaluating the results of several screening assays, each of which has some level of false results and, accordingly, each of the screening assays would be a 'diagnostic assay'. Therefore, to enable a diagnostic assay use, a disclosure merely needs to teach how to make and use the assay for screening purposes." "Training materials for Examining Patent Applications with Respect to 35 USC Section 112, First Paragraph Enablement of Chemical/Biotechnical Applications" http://www.uspto.gov/patents/law/1pecba.jsp#iiia2 (last visited February 28, 2011)

Here, the Examiner in deciding enablement requires a showing essentially that a claimed method of diagnosis must in and of itself be used to diagnose a condition. Therefore, the Examiner has failed to follow these guidelines.

For example, the Examiner states that "[w]hile the applicants provide evidence of increased IL-8 expression in OSCC subjects, these increased levels are not present in all of the subjects, and there is no indication of how these changes, *alone*, would be correlated with diagnosing cancer." (Emphasis added). The Examiner surmises that "it is highly unpredictable to use altered

expression data for the purpose of *specifically* diagnosing cancer." (Emphasis added). And the Examiner concludes "[o]ne wishing to practice the presently claimed invention would have to produce additional experiments to determine how (or if) changes in expression of a single gene could be used to *specifically* diagnose OSCC." (Emphasis added).

Thus, while the Applicants have described a screening assay arguable and in as much satisfied the enablement requirement, the Examiner is requiring a showing that the claimed diagnostic methods "alone" can be used to "specifically diagnose" cancer. This clearly contradicts the teachings of the examination training materials and the applicable standard as described.

Therefore, because the Examiner has based the enablement rejection on an incorrect standard, its withdrawal is respectfully requested.

In addition to failing to apply the appropriate standard in determining enablement, the Examiner has also failed to consider all the evidence as required in considering the level of predictability present in the art. "The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole." "Training materials for Examining Patent Applications with Respect to 35 USC Section 112, First Paragraph Enablement of Chemical/Biotechnical Applications".

The Examiner makes the supposition that the "[d]iagnosis of cancer (or oral cancer/OSCC) by correlating with gene expression is highly unpredictable" based on a reading of several references including Sun *et al.*, Ziober *et al.*, and Westra and Califano.

For example, the Examiner reads Sun *et al* as underpinning the notion that "while gene expression data and microarray analysis show promise as analytical tools, its clinical applications are still questionable." Office Action, page 5, first full paragraph. In support, the Examiner cites a passage from Sun *et al* that begins "(a) [t]here is a significant overlap for clinical outcome prediction between gene expression profiles and pathogenic features, and most studies have not shown a superior performance using the new technology [microarrays] over conventional predictors . . ."

So, while Sun *et al* point to the clinical utility of microarray assays "t]here is a significant overlap for clinical outcome prediction between gene expression profiles and pathogenic features," the Examiner has taken the position apparently that the instant invention is not enabled because its performance, based on the opinion of Sun *et al,* may not be superior to conventional methodologies. However, a showing of "superior performance" as defined by Sun *et al.* is not the standard used in assessing patent enablement.

The instant invention does possess attributes not considered by Sun *et al.*. For example, current methodologies of cancer screening are often invasive, involving the isolation of blood or serum and require persons with specialized training (phlembotomist). In comparison, the isolation of saliva is relatively non-invasive and can be acquired by persons without specialized training offering an advantage over conventional methodologies.

A careful review of these references reveals the following passages concerning gene expression profiling and correlation with disease. Sun *et al* states succinctly: "There is a significant overlap for clinical outcome prediction between gene expression profiles and pathologic features." *Cancer Epidemiol. Biomarkers Prev.* 15:2063-2068, 2067, para. 1. Ziober describes "[g]ene expression profiles [as] hav[ing] shown dramatic correlations with tumor development and progression." Head & Neck (2008) 30:111-121, 114, left hand column, first full paragraph. And finally, as to the Applicants' work, Westra and Califano conclude that "[t]he work of Li *et al* opens a new avenue for the early detection and intervention of oral cancer." *Clinical Cancer Res.* (2004) 10:8130-8131, 8131, first full paragraph.

Thus, reviewed in whole, the cited art suggests that gene expression profiles can be used as predictable screening tools in disease diagnosis.

Accordingly, the Examiner should withdraw the enablement rejection in so much as the Applicants have satisfied the applicable standard; they have taught an art recognized (Westra and Califano) method for early cancer detection.

III. Rejection under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 10 to 13 and 28 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking written description. Without conceding the propriety of this rejection, Applicants have amended independent claim 10, in part, to methods of diagnosing a cancer of the oral cavity and/or oropharynx, the method utilizing changes in the mRNA profile of a group of genes including IL8, DUSP1, H3F3A, OAZ1, S100P and SAT. Applicants respectfully submit that the amended claims fulfill the written description requirement for the reasons expressed below.

"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." "Written Description" Requirement, Federal Register, 66(4):1099-1111 (2001). "Possession may be shown in many ways. For example, possession may be shown, *inter alia*, by describing an actual reduction to practice of the claimed invention." *Id.*

As the Examiner readily admits, the instant specification describes the actual reduction of practice of the claimed method. ("The instant specification teaches that there is a correlation between the expression of a group of specific genes with oral squamous cell carcinoma." Office Action, page 9, second full paragraph). Thus, the Applicants were in possession of the claimed invention, a method of diagnosis through the application of gene expression profiling. Accordingly, Applicants have satisfied the written description requirement.

In support of the written description rejection, the Examiner relied upon *University of Rochester v. G.D. Searle & Co.*, Office Action, page 10, the facts of which are clearly distinguishable from those here. 69 USPQ2d 1886. In *Rochester*, the inventors patented a method of treating a disease by the use of inhibitor of a particular enzyme. The inventors in that case had taught an assay for finding such inhibitors, but had found and described none. It was unknown whether any inhibitors with the claimed properties even existed or could be made.

In the instant application, Applicants have claimed methods for diagnosing diseases and conditions. In the Examples, Applicants provide detailed protocols describing the claimed methods. Further, Applicants have identified a number of transcripts whose expression patterns

are indicative of a disease, for example those associated with IL8, IL1B, DUSP1, H3F3A, OAZ1, S100P, and SAT. These transcripts are chemicals with an art recognized structure (for example, sequences). Thus, Applicants have provided a "structure, formula, or chemical name" of exemplary substances in satisfaction of the written description requirement.

Accordingly, the instant application is clearly distinguishable from the patent at issue in *Rochester* where none of the claimed materials had been described. Thus, the Examiner's reliance on Rochester as supporting a finding that the instant application is misplaced and the written description rejection should be withdrawn.

For the reasons expressed, Applicants respectfully request the Examiner withdraw the rejection for lack of written description.

IV. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 10 and 28 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Specifically, the Examiner alleges that the terms "the RNA profile" and "the saliva" as they appear in claim 10 and the phrase "wherein detecting a transcriptome pattern" in claim 28 lack sufficient antecedent basis. Further, the Examiner alleges that "it is unclear how a transcriptome pattern can be obtained from an mRNA profile of a single gene. (Emphasis in original).

While not conceding to the propriety of these rejections, Applicants have amended claims 10 and 28, as depicted below, thereby rendering these rejections moot.

Claim 10 as amended recites, in part, "providing a ~~cell-free fluid phase portion of the~~ saliva supernatant from ~~of~~ the subject;
detecting in the ~~provided cell-free~~ saliva supernatant ~~fluid phase portion~~ an mRNA profile of a gene associated with the pathology, disease or disorder; and

comparing the mRNA profile of the gene with a predetermined human mRNA profile

Claim 28 as amended recites, in part, "wherein detecting an mRNA profile ~~transcriptome pattern~~ is performed by microarray assay, high density oligonucleotide microarray assay, quantitative PCR or RT-PCR..

V. Rejection under 35 U.S.C. § 102(b)

Claim 10 stands rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Gocke *et al.* (U.S. Patent No. 6,511,805). Applicants respectfully disagree.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131.

Amended claim 10 provides, in part, "detecting in the saliva supernatant an mRNA profile of a gene associated with the pathology, disease or disorder; and comparing the mRNA profile of the gene with a predetermined human mRNA profile of the gene, [and] the predetermined human mRNA profile . . ."

According to the Examiner, Glocke *et al* teaches "a method for diagnosing [a] malignancy comprising providing a cell free biological sample, such as saliva, detecting mRNA expression of a papillomavirus gene, comparing it to a positive control containing the gene of interest (i.e.: a predetermined mRNA profile of the gene)." Thus, Glocke *et al* teach detecting viral gene expression but not "comparing the mRNA profile of the gene with a predetermined *human* mRNA profile."

As such, Glocke *et al* fail to teach each and every aspect of the claim 10. Therefore, Glocke *et al* does not anticipate claim 10 and the rejection based on alleged lack of novelty under 102(b) should be withdrawn.

VI. Rejection under 35 U.S.C. § 103

Claims 10-13 and 28 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kopreski *et al.* (2000; U.S. Patent No. 6,607,898), Kopreski *et al.* (2001; U.S. Patent No. 6,759,217), and Squire *et al.* (2002; *Head and Neck*, Vol 24, pp. 874-887). Applicants respectfully disagree.

The instant claims are drawn, in part, to a method of diagnosing a disease or disorder based on the comparison of an mRNA profile generated from a cell-free fluid phase of saliva with a predetermined human mRNA profile thereby diagnosing a disease or disorder. The Applicants have identified IL-8 as a diagnostic marker of cancer.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP 2142. A rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than *predictable results*. *KSR International v. Teleflex Inc.*, 82 USPQ2d 1385 (2007)(Emphasis added). If any of these findings cannot be made, then this rationale cannot be used to support a conclusion of obviousness. MPEP 2143 A.

The Examiner identifies three references as rendering the instant claims obvious: Kopreski *et al.* (US6,607,898; '898), Kopreski *et al.* (US6,759,217; '217) and Squire et al. (2002) Head & Neck 24:874-887 ("Squire"). The Examiner alleges that '898 teaches a method of diagnosing cancer using a cell free biological sample, such as saliva and that '217 teaches quantification and comparison of the amount of extracellular mRNA present in a sample. The Examiner readily admits that neither of these references suggests the use of IL-8 as a biomarker for cancer.

The Examiner relies on Squire to fill this omission, alleging that Squire teaches up-regulation of IL-8 mRNA in head and neck cancer.

Thus, when taken in whole the Examiner alleges that these teachings render the instant claims obvious because the substitution of the marker taught by '898 with IL-8 as taught by Squire "would have yielded predictable results of screening IL-8 in saliva of OSCC patients."

The flaw with the Examiner's reasoning is that none of the cited references teach or suggest that the expression profile observed in cellular fractions is the same as that in non-cellular fractions. For example, while both the '898 and '217 references discuss cell free biological samples and the detection of RNA, neither teaches nor suggests that the expression profiles in saliva supernatant would be the same as in cellular fractions. On the other hand, while Squire may have observed changes in IL-8 expression between normal tongue and tongue tumor, there is no teaching or suggestion that the expression profile observed by Squire would correlate to the expression profile in saliva supernatant. Thus, taken in whole there is no suggestion to look at IL-8 expression in saliva supernatant.

Thus, it is not predictable based on the combination of '898, '217, and Squire that IL-8 found in saliva supernatant could be used in screening for oral cancers. Accordingly, the Examiner has failed to establish that the invention is obvious in light of the cited art and the rejection of the claims as obvious should be withdrawn.

VII. Rejections under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 10, 13, and 28 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 4, 7 to 12, 14, 15, 17, and 20 of copending Application No. 12/468,766.

Claims 10 and 28 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 3, and 7 to 10 of copending Application No. 12/475,347.

Applicants respectfully request that these rejections be held in abeyance until such time as they are the only rejections remaining. MPEP 822.01.

CONCLUSION

All the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310 (Docket Reference: 008074-5002-US).

Prompt and favorable consideration of this Amendment and Response is respectfully requested.

Respectfully submitted,

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